How does stress, depression and anxiety affect patients undergoing treatment?

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Structured abstract:

Purpose of review: To review latest findings about the impact of fertility care on emotional distress and its effect on treatment outcome.
Recent findings: Treatment failure and long agonist protocols are associated with increased emotional distress during treatment. Screening tools can be used to identify men and women at risk of emotional maladjustment at the start of fertility treatment and people unlikely to need emotional support during or after treatment. There are inconclusive results about the association between emotional distress and outcome of fertility treatment. Systematic review of studies evaluating the effect of psychological and educational interventions on anxiety, depression and live birth (or ongoing pregnancy) are uninformative due to clinical heterogeneity and risk of bias.
Summary: ART is emotionally demanding, patients likely to adapt more poorly can be identified in advance, and fertility staff could follow good practice guidelines followed to provide them with support during treatment.

Keywords: infertility, psychological intervention, screening, anxiety, depression

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Introduction

Managing emotional distress (anxiety, depression, perceived [infertility] stress) is an important aspect of fertility care. Increasingly, this type of psychosocial care is expected to be evidence based, and provided by fertility clinic staff through patient centred care, and not just referral to specialised counsellors (1,2). This selective review will examine recent psychological studies that inform on provision of psychosocial care.

1. Infertility, infertility treatment and emotional distress

Emotional distress in infertility patients has been attributed to the unfulfilled wish for a child, stigma of underlying conditions (e.g., hirsutism), limiting physical aspects (e.g., severe pelvic pain), treatment procedures (e.g., ovarian stimulation) and events (waiting for pregnancy test) (3). Two systematic reviews confirm past research in showing the effect of treatment failure on wellbeing of men and women (4, 5, both 12 studies). In addition to showing effects in women, these also showed that men's psychological adjustment could deteriorate during fertility treatment (5) especially in response to treatment failure (5). Avoidance, catastrophizing and poor partner support was associated with poor adjustment in men (5). Depression and anxiety lessened over time (4) with a return to baseline probably occurring between six (5) and 12 months (4) after fertility care. Toftager et al. (6) reported physical (feeling bloated, abdominal pain), emotional (e.g., unexpected crying) and behavioural (e.g., poor quality sleep symptoms were more likely and intense in women randomly assigned to long gonadotrophin agonist (LGA) protocols than short antagonist (SA) protocols. This extra burden could explain why patients having up to three natural cycle ART reported more satisfaction with treatment and less depression after treatment than patients having undergone a single cycle with LGA (7).

One important source of heterogeneity in studies on the impact of infertility treatment is measurement inconsistency. A recent Cochrane review reported the use of more than 30 different measures in the psychological literature aimed at improving wellbeing (8). Using the same measure consistently could address this problem. Recently, a review (9) and an empirical study (10) examined the psychometric properties of the most frequently used measures of infertility-specific patient reported outcomes (i.e., Fertility Quality of Life, FertiQoL [11], Fertility Problem Inventory, FPI [12], Copenhagen Multicentre Psychosocial Infertility-Fertility Problem Stress Scale, COMPI-FPSS [13]). Both studies concluded that the three measures had satisfactory psychometric properties (9,10). There were advantages specific to each measure but equally there were gaps in psychometric testing for all measures, for example, lack of a clinically important difference (9). Choice of tool should match the situation (9, 10). FertiQoL (24-items) is best for overall quality of life measurement, especially in treatment, is sensitive to the effects of interventions, and potentially useful for prediction of anxiety and depression. The Fertility Problem Inventory (34 items) is best for decision making and

longer term adjustment because it assesses beliefs known to be relevant to adapting to childlessness (14). The COMPI-FPSS (14 items) is a coherent measure of perceived infertility stress and its brevity and link to the concept of stress make it useful for studies stress, coping and clinical outcomes (e.g., pregnancy rate).

2. Emotional distress and its relationship to treatment outcome

Many people think that emotional distress due to fertility problems or other stressors interferes with the success of fertility treatment. Although these beliefs are congruent with stress theories and non-human animal research, evidence in humans is not compelling.

Two recent systematic reviews and meta-analyses in ART samples (with overlapping studies) examined prospective studies on this association in ART. Nicoloro-SantaBarbara et al. (15) included 20 studies evaluating the association between anxiety, depression or perceived stress and verified pregnancy (blood test, ultrasound scan, live birth) in women undergoing IVF or ICSI. Pooled effect sizes for anxiety or depression measured before or during treatment (four separate analyses) revealed small non-significant effect sizes between outcome groups. A similar non-significant pooled effect size was obtained for perceived stress. None of the moderators were significant in explaining heterogeneity which ranged from 35% to 78%. In contrast, Purewal et al. reported significant associations between treatment outcome and anxiety and depression measured pre-treatment (16) and during treatment (17) in women undergoing ART. Meta-analysis of pre-treatment data (22 studies) showed a small significant negative effect size (SMD) for depression and anxiety. Meta-analysis of emotional distress during treatment (from pre-treatment to embryo transfer) (11 studies) also showed significant, negative pooled effect sizes with effects being smaller when only IVF patients (not ICSI) and recent studies (since 2010) were considered. The difference in results requires explanation especially for distress during treatment where Purewal et al. (17) reported effect sizes double those reported in Nicolo-SantaBarbara et al. (15) despite similar study selection criteria.

Purewal et al. (17) included an additional six studies and these generally had higher effect sizes than the other studies overlapping with Nicolo-SantaBarbara, making this a likely explanation for the difference in results. However, there were inexplicable choices in Purewal (17) too that could have produced larger effect sizes during treatment (e.g., allocation of a large 'pre-treatment' effect size to 'during treatment' analysis). Even if effect sizes do prove to be of that size during treatment it is unlikely these would indicate that being stressed or distressed during treatment reduced the chance of pregnancy because of confounding. Ratings taken at oocyte retrieval or embryo transfer (i.e., during treatment) will strongly reflect knowledge about the quantity and quality of oocytes and embryos produced, which highly predict treatment outcome.

A lack of consistent association between meta-analyses could be due to the poor explanatory power of the simple associative model used, where emotional distress is the only risk factor considered. More complex models that take into account biomedical (e.g., prognostic indicators) and behavioural risk factors (e.g., smoking, caffeine) that vary with emotional distress could probably improve its prediction for treatment outcome. However, if complex models are developed these should focus on risks that benefit ART outcomes when modified. A recent systematic review and meta-analysis (18) demonstrated that preconception lifestyle interventions based on caloric restriction and exercise were effective in stimulating weight loss (about 3.5 kg) and BMI status change (about one-point change) but these losses only produced a higher pregnancy rate in people achieving pregnancy without ART and not in those undergoing ART (18).

It has been argued that, in any case, supraphysiologic effects of stimulation and mechanical procedures of oocyte retrieval and embryo transfer would compensate for any effects of emotional distress on ART treatment outcome obscuring any true association between stress and fertility. However, even among infertile people in the general population (i.e., non-clinical sample) emotional distress is not associated with eventual pregnancy (19). In a Norwegian registry study, infertile women from the general population with and without clinical levels of emotional distress were followed up to determine whether they would achieve pregnancy (19). The results showed that 20.1% of women scored above the clinical cut-off for anxiety, 7.7% for depression, and 22.2% for either. Follow-up was complete (0% attrition due to register). The live birth rate was overall 28.7% and was not significantly different in women with clinical levels of emotional distress: 32.7% in women with high anxiety, 33.0% high depression, 27.6% both high anxiety and depression). Authors counter-argued alternative explanations on the grounds of controlling confounders and power.

These two meta-analyses do not provide clarity on the association between anxiety and depression in women undergoing ART.

4. Early detection of emotional distress

Early detection of emotional distress could help clinics provide preventative support at the start of treatment. The SCREENIVF was developed to identify people with emotional maladjustment before treatment and later during or after treatment outcome (20). It detects risk based ratings of depression, anxiety, helplessness, acceptance of infertility and social support. Past research showed that SCREENIVF had satisfactory sensitivity and specificity but this finding was based on using overlapping items in the detection and outcome tools, a limitation that could inflate predictive validity. The concurrent and predictive validity of the SCREENIVF was recently tested using different items in 913 Dutch men and women undergoing ART. SCREENIVF and emotional maladjustment (self-reported Hospital Anxiety and Depression Scale, HADS) were measured at the start of stimulation before the first scan (21). The HADS was completed again 10 days and six weeks after embryo transfer (corresponding to waiting period for pregnancy test and

post-results, respectively). Results showed that concurrent validity (cross-sectional prediction from SCREENIVF to HADS) was better than predictive validity (prospective prediction from SCREENIVF at start to HADS-Day 10 or HADS-six week). Furthermore, SCREENIVF was better at predicting those not at risk then those at risk of emotional maladjustment. These results mean that staff using SCREENIVF could feel confident that if patients were categorised as "not at risk" at the start of treatment then it would be very unlikely that they would have emotional maladjustment later. However, staff should have less confidence that those rated as "at risk" would have emotional maladjustment during those later periods. Poor prediction was attributed to low base rate for maladjustment in infertile populations. It was also attributed to the problem of missing predictors, namely pregnancy status at the predicted time of risk (e.g., six weeks after treatment outcome). To improve positive predictive values it was suggested that the SCREENIVF algorithm be adjusted to include prognostic indicators (e.g., age) (21).

3. Impact of intervention studies on emotional distress in people with infertility

Supporting patients during treatment could improve wellbeing during treatment and counter any negative effects of emotional distress on treatment outcome and trajectory (if these exist). Several reviews have sought to synthesise this research but only recently was a Cochrane review carried out (Verkuijlen et al. 8). The review examined psychological and educational interventions in infertility (39 RCTs, 4925 participants). The set of primary outcomes were anxiety, depression, live birth, and ongoing pregnancy (20 weeks). Psychological interventions were named therapies (e.g., mind-body program) and therapies focused on changing behaviour, cognitions or emotional impact of infertility and fertility care. Educational interventions were geared toward improving self-management and self-efficacy (e.g., better coping) through education about infertility and its treatment and relevant psychosocial strategies (e.g., coping skills training, psycho-education). The review concluded that data could not be pooled across intervention studies because of too high risk of bias (especially from lack of blinding and high attrition) and too high clinical heterogeneity in participant characteristics, nature of interventions and delivery characteristics. Indeed, all studies had high risk of bias on at least one domain, and 50% had risk of bias for blinding and attrition. Further, the included studies evaluated more than 25 different interventions (e.g., hypnosis, music therapy, cognitive behaviour therapy, stress management, informative leaflets) delivered in many ways. Summary data was presented for the primary outcomes but the authors warned that effects, especially benefits, should be considered with extreme caution because the biases "resulted in exaggerated and implausible odds ratios" (Verkuijlen et al. [8], p. 26). Consequently, the evidence was generally downgraded to very low quality evidence, and a plea made for more rigorous designs.

Conclusions

Increasingly, fertility clinic staff will be called upon to provide evidence-based

psychosocial care. To do so they will require knowledge of the emotional impact of treatment, the effect emotional distress can have on treatment trajectories and outcomes, and the interventions staff can use to deliver psychosocial care within the constraints of their clinical duties. Three main themes emerged from this review. First, more rigorous and homogenous experimental designs are needed to improve quality of psychological research. Consistently using one of the infertility patient reported outcomes (FertiQoL, Fertility Problem Inventory, COMPI-FPSS) and improving trial design in intervention evaluation studies (especially use of attentional control groups and follow-up) would help. Evaluation should be concentrated on replicating effects of existing, theory driven psychological and educational interventions and mechanisms of action rather than on development of more interventions. Second, we need more research on the experiences of men in treatment because they too suffer from infertility and its treatment. Men are only partially represented in intervention studies (usually as part of couple), and virtually absent from research on the effect of emotional distress on treatment outcome and trajectories despite being integral for both. Third, the emotional demands of treatment and protocols are significant. Patients should be informed in advance of the burden of particular drug protocols and the period of emotional distress that ART could involve so they can integrate these in decision-making about treatment. Men should not be neglected in discussions of psychosocial implications of treatment. Finally, staff should screen people at the start of treatment (e.g., using SCREENIVF) to identify those already distressed at the start but also those unlikely to need additional support later so psychosocial resource are directed to those that need it most. The evidence base for effective interventions is not yet informative but psychosocial guidelines for fertility staff not specialised in psychosocial care exist (1) and these could be used to guide good practice until better quality evidence is published.

Key points

- ART treatment failure are emotionally demanding for women and men, and more so for and specific types of protocols on women
- Patients experiencing distressed at the start of treatment and those unlikely to need additional support resources can be identified pre-treatment
- There is no compelling evidence for an association between emotional distress (anxiety, depression, infertility stress) and treatment failure in ART
- The RCTs evaluating the benefits of psychological and educational interventions in fertility care are uninformative because clinical heterogeneity and too high risk of bias (blinding, attrition, attentional controls)

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employer of J. B. (Cardiff University) could one day receive royalties from the commercial use of Fertility Quality of Life (FertiQoL). J.B. could one day receive royalties from the commercial use of Fertility Quality of Life (FertiQoL). However, both of these are unlikely because FertiQoL is freely available for practice and research.

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